

IN THE U.S. PATENT AND TRADEMARK OFFICE

In re application of

Véronique Coxam

Confirmation No: 6839

Application No. 10/552,723

Art Unit: 1611

Filed on October 11, 2005

Examiner: Barbara Frazier

NUTRITIONAL OR THERAPEUTIC COMPOSITION CONTAINING THE COMPOUND
OLEUROPEIN OR ONE OF THE DERIVATIVES THEREOF

DECLARATION OF VERONIQUE COXAM UNDER 37 C.F.R. §1.1.32

Assistant Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Véronique Coxam, hereby declare as follows:

1. I am the first inventor named of the above-identified U.S. application

2. My educational and professional experience is presented in the curriculum vitae attached hereto (Exhibit 1). I have been employed by the Institut National de la Recherche Agronomique (INRA) as a researcher since 1990. I have been at the head of the Laboratory Unit entitled "Alimentation, Squelette et Métabolismes" ("Nourishment, Skeleton and Metabolisms"), previously called "The Osteoporosis team", which

NC

belongs to the Research Unit "Nutrition Humaine" ("Human Nutrition") of Clermont-Ferrand/Theix, since 1997, and the deputy head of the Research Unit "Nutrition Humaine" since 2007. My main area of research relates to the nutritional prevention of osteoporosis.

3. As the first inventor of the above-identified patent application, I am familiar with the whole subject matter that is described and claimed therein.

I understand that the pending set of claims contains claims 1, 2, 4, 5, 7-14, 16, 19, 21-23 and 25-26. The main claim is claim 1. I understand that the pending set of claims, more precisely claim 1, is currently amended.

Claim 1 relates to a method for stimulating bone formation and/or bone resorption in humans or animals suffering from unbalanced bone formation-bone resorption ratio, the said method comprising the administration of a composition comprising oleuropein as active compound.

4. I have carefully studied and I am familiar with the Fourth Office action dated of November 16th, 2010. I have understood that the Examiner took into consideration all the pending claims which thus form the basis of her rejection.

5. I have also understood that, in page 9, the Examiner has rejected the present invention as being obvious over Lockwood (US7445807) combined with Nachman (US5714150).

6. I have further understood that, in page 3 of the Office Action, the Examiner has rejected the present invention as being anticipated over Hamdi et al. (US2003/0004117).

7. Concerning the rejection based on Hamdi, I have noticed that the Examiner is of the opinion that Hamdi, which provides a method for treating angiogenesis, also describes the claimed method: The Examiner argues that the patients to whom the compositions of Hamdi are administered are the same persons as those of the claimed method since the patients of Hamdi would necessarily seek to prevent bone loss occurring to and/or seek to prevent a disorder associated with unbalanced bone-formation-bone resorption ratio.

8. Concerning the rejection based on Lockwood and Nachman, I have understood that the Examiner believes that Lockwood combined with Nachman makes obvious the claimed method since:

(i) Lockwood describes nutritional supplements to be administered to a various types of person including postmenopausal women who are known to be particularly susceptible to osteoporosis. The said nutritional supplements may comprise edible plant extracts which may include olive leaf; and

(ii) Nachman describes a method for obtaining an olive leaf extract comprising oleuropein and that oleuropein has antiviral property.

To the opinion of the Examiner, such facts would motivate practitioners to use the extract of Nachman for preparing the nutritional supplement of Lockwood and to administer the resulting nutritional supplement to a large variety of persons. I have understood that the Examiner believes that the administration of the supplement of Lockwood to a person would necessarily imply the induction of bone formation or the inhibition of bone resorption, which would inherently anticipate the claimed method.

I have further noticed that the Examiner is of the opinion that as in the case of Hamdi, the population targetted by Lockwood is the same that of the instant invention.

9. I have studied and I am familiar with the documents cited by the Examiner. As one ordinary skill in the art, I have understood the main objects and the main concepts described in each document cited by the Examiner.

10. I respectfully disagree with the rejections raised by the Examiner. As one ordinary skill in the art, I would consider that all the cited documents do not describe or make obvious the claimed invention.

11. I respectfully disagree with the rejection based on Hamdi for the following reasons:

Firstly, I have understood that Hamdi showed that oleuropein enables to inhibit angiogenesis through chick chorioallantoic membrane assay and adult mouse ear model. Based

on these experimental results, Hamdi provides the use of oleuropein for inhibiting angiogenesis in a patient suffering from diseases such as cancers, ocular diseases and inflammations conditions. As one ordinary skill in the art, I know that (i) angiogenesis and (ii) bone metabolism are controlled by distinct biological pathways so that the oleuropein activity on metabolism cannot be extrapolated from its activity on angiogenesis. Consequently, to my understanding, Hamdi does not contemplate the use of oleuropein for restoring bone metabolism equilibrium when describing the administration of oleuropein for inhibiting bone resorption.

Secondly, I would like to underline that the need for inhibition of bone resorption and/or induction of bone formation are not universal among human beings. Some genetic diseases involve alteration of bone resorption. In particular, Osteopetrosis ("marble bone disease") which refers to heritable disorders of the skeleton characterized by increased bone density results from abnormalities in osteoclast differentiation or function and more precisely from the inability of osteoclasts to properly resorb immature bone (For illustration, see Exhibit 2, Wilson et al., Orphanet Encyclopedia, 2003, 1-6 and more precisely abstract and part entitled "etiology").

For patients suffering from osteopetris, the inhibition of bone resorption and/or the induction of bone formation may be

detrimental. Thus, it cannot be stated that everyone needs induction of bone formation or inhibition of bone resorption.

Thirdly, when considering the change in bone mass in most people as a function of age, one can distinguish three main phases:

(i) a rapid increase of bone mass to the peak bone mass. This phase mainly correlates with the growth period,

(ii) a steady state of bone mass observed in the beginnning of adulthood (typically between 25 and 35 years) : in this phase, bone mass is constant thanks to equilibrium between bone formation and bone resorption , and

(iii) a loss of bone mass with age generally after 40 years. The bone mass decrease may be rapid for women around the menopause. This bone loss results from bone remodeling unbalance involving (i) a decrease of osteoblastic activity and/or (ii) an increase of osteoclastic activity.

As quoted by the Examiner, the patients of Hamdi suffer from various diseases such as cancers, ocular diseases and inflammatory conditions. Said diseases are mostly unrelated to an unbalance of bone metabolism and can affect a large variety of people independently of their bone status and their age. In particular, said people may suffer from (i) genetic diseases such as osteopetrosis for which the induction of bone formation and/or the inhibition of bone resorption may be detrimental or (ii) may not experiment an unbalanced bone metabolism.

In other words, I strongly believe that a significant part of Hamdi's patients does not suffer from unbalanced bone formation/bone resorption ratio, as stated in current claim 1.

12. Concerning the rejection based on Lockwood and Nachman, I respectfully disagree with the reasoning discussed above in item 7.

13. Firstly, I would like to underline that the invention is not a nutritional supplement comprising oleuropein but a method for inducing bone formation or inhibiting bone resorption in a patient suffering from an unbalanced bone formation/bone resorption ratio. As in the case of Hamdi, such a method is contemplated neither by Lockwood nor by Nachman.

Firstly, to my understanding, Lockwood describes nutritional supplements which may contain a large type of ingredients such as proteins, carbohydrates, vitamins, minerals and eventually edible plant extracts for supplementing the nutritional needs of various types of individuals. In the part entitled "Background of the invention", Lockwood cites vitamin D, soy isoflavones and minerals, namely boron, calcium and manganese, as appropriate nutrients for maintaining bone health or reversing osteoporosis. Lockwood never expressly contemplates the use of olive leaf extract or that of oleuropein for maintaining bone health. I have further noticed that Lockwood indicates neither the biological activities of olive leaf extract nor the composition of the said extract in terms of active

compounds. More precisely, the olive leaf extract is merely mentioned as a potential edible plant extract among a long list of extracts which may be used for preparing the dietary supplement (see col.4 l.30-39)

To my understanding, Nachman relates to a method for extracting oleuropein from olive leaf. Nachman suggests that oleuropein may be used for treating malarial infection and some viral or bacterial diseases (see column 1, part entitled Background of the invention). Like Lockwood, Nachman does not describe that oleuropein may have some activities on bone metabolism.

Thus, as one of ordinary skill in the art, I would have not considered that Lockwood and Nachman are relevant in respect to the claimed method since these documents do not contemplate the use of oleuropein for inducing bone formation and/or inhibiting bone resorption in a patient in need thereof.

Moreover, the nutritional supplements of Lockwood may be administered to a large variety of people which may implicitly encompass people suffering from (i) genetic diseases such as osteopetrosis or (ii) having a balanced bone metabolism. Thus, as in the case of Hamdi and contrary to the Examiner's statement, the people targeted by Lockwood do not necessarily represent the the same set as that of the present invention.

14. Secondly, I strongly disagree with the fact that in view of Nachman, the one skilled in the art would select olive

leaf extract as the edible plant extract for preparing the nutritional supplement of Lockwood in order to improve the overall health. I also disagree with the argument that the administration of said nutritional supplement to a person according to Lockwood inherently discloses the claimed method since it would necessarily induce bone formation and/or inhibit bone resorption.

Actually, when reading Lockwood, as one of ordinary skill in the art, I understand that the plant extract is not an essential component of the nutritional supplement since its presence is optional (see col. 10, 1.4-1.5: "approximately 0 to 1 percent by weight edible plant extracts" and see col. 15, 1.54-1.65 wherein a nutritional supplement for children and adolescents which does not comprise plant extract is described). Noticeably, the nutritional supplement of Lockwood dedicated to older adults (who are susceptible to osteoporosis as stated by the Examiner) does not comprise a plant extract such as an olive leaf extract (see col.18 1.37-1.52).

I further understand that the aim of the nutritional supplement of Lockwood is to supplement nutritional intake of individuals such as older adults, children and individuals engaged in bodybuilding (See col 8 1.11-1.24). As mentioned above, Nachman only mentions that oleuropein may be used for treating infectious diseases. To my understanding, the fact that oleuropein may be an anti-infectious agent is no incentive for

use in order to supplement nutritional intake which is the aim sought by Lockwood. As a consequence, as one of ordinary skill in the art, if I had to prepare a nutritional supplement according to Lockwood, it would be unlikely that I would specifically introduce in said nutritional supplement an extract of olive leaf and in particular, an oleuropein-enriched one, even considering Nachman.

I thus believe that there is no specific reason for the nutritional supplement of Lockwood to necessarily contain an olive leaf extract. Consequently, the administration of said supplement to a person does not necessarily reproduce the claimed method by inherency.

15. Thirdly, I strongly disagree with the Office Action statement saying that olive leaf extract inherently contains oleuropein.

As a person skilled in the art, I know that the presence of oleuropein in extracts obtained from olive leaves depends on the parameters of the extraction process used such as temperature, pH and solvents and also on the origin and the conditioning of olive leaves. I also know that the oleuropein is a compound sensitive to temperature, hydrolysis, enzymatic degradation and oxidation, which may have a direct impact on its presence in an extract.

Such facts are well-documented in scientific and patent documents published before or after the filing of the present

application. To support the above developped arguments, I would like to cite several scientific publications that I believe reliable.

For example, Ansari et al. (Exhibit 3 see Fig 3 p.44), Lee et al. (Exhibit 4 see table 1 p.6110) and Altiok et al. (Exhibit 5 see Figure 4 p.345) show that the choice of the solvent of extraction has a direct impact on the final presence of oleuropein in the leaf extract since certain conventional solvents such as n-hexane, dichloromethane, methanol and water at ambient temperature are poorly efficient and even totally inefficient to extract oleuropein. The temperature and the pH are also important parameters for the extraction: for example, deionized water at 60°C enables to extract a significant content of the oleuropein present in olive leaves wherein deionized water at ambient temperature is ineffective. I have noticed that Nachman herself mentions that high temperature of extraction may induce oleuropein degradation during the process she described (see 1.6-1.8 col.2).

Ortega-Garcia et al. (see Exhibit 6) and Ansari et al. further describe that the oleuropein content of olive leaves greatly varies depending on ripening (see Figure 7, p.52 of Exhibit 6) and geographic origin (see Table 1 p.39 of Exhibit 3). As illustrated by Malik et al. (Exhibit7), the method for preparing olive leaves in view of a subsequent process of extraction may also greatly impact the amount of oleuropein in

the final extract: The air-drying of olive leaves above ambient temperature or their freezing followed by their thawing at ambient temperature induces a significant degradation of oleuropein present in the olive leaf: the loss of oleuropein may thus account for more than 95% of its initial amount in olive leaf (see Figure 1 p.9 of Exhibit 7). In this respect, I would like to underline that the freezing is a conventional method for the storage of vegetal raw materials.

Consequently, in view of my research experience and my knowledge of the state in the art, I strongly believe that depending on (i) the origin of olive leaves, (ii) the method for preparing olive leaves, (iii) the extraction process performed (in particular the solvent chosen) and/or (iv) the condition of storage of the resulted extract, it is possible to obtain an olive leaf extract which does not contain oleuropein through the implementation of various methods.

Last but not least, Lockwood does not indicate what kind of olive leaf extract to use for preparing its nutritional supplement and never mentions oleuropein as a compound of interest. In this respect, I would like to remind that olive leaves contain various compounds such as caffeic acid, p-coumaric acid, vanillic acid, vanillin, luteolin, diosmetin, rutin and vitamins which are or are likely to be useful for therapeutic or nutritional applications.

I thus believe that the nutritional supplement of Lockwood does not necessarily contain oleuropein.

13. I declare that all statements made in this declaration of my knowledge are true and that all statements made on information and belief are believed to be true and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Signed at Theix, France



Véronique Coxam

this 28th of April 2011

ENCLOSURES:

- Exhibit 1: Curriculum vitae of Véronique Coxam
- Exhibit 2: Wilson et al., Orphanet Encyclopedia, 2003, 1-6
- Exhibit 3: Ansari et al., Journal of the Iranian Chemical Society, 2011, 8, 38-47
- Exhibit 4: Lee et al., Biosource Technology, 2009, 6107-6113

- Exhibit 5: Altiok et al., Separation and Purification Technology, 2008, 342-348
- Exhibit 6: Ortega-Garcia et al., Tree Physiology, 2008, 28, 45-54
- Exhibit 7: Malik et al., Journal of Food, Agriculture & Environment, 2008, 6(2), 8-13